REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on July 26, 2002. Claims 1-30, 32-52 and 57-59 were cancelled previously. . Claims 60-63 have been added. Claims 31, 53-56, and 60-63 are pending.

A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I.

Claim amendments were made to better define one embodiment of the invention, notwithstanding the Applicants' belief that the unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, for the purpose of furthering Applicants' business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals. None of the amendments to the claims is related to the statutory requirements of patentability unless expressly stated so herein. Applicants reserve the right to prosecute the originally filed claims in the future. The comments in the Office action are now addressed in turn.

Status of the Case

As an initial matter, Applicants note that a preliminary amendment was filed on November 28, 2000 as evidenced on the Transmittal and on the Post Card. Copies of the Preliminary Amendment as filed, the Transmittal and Post Card are enclosed. Applicants further note that the Filing Receipt, mailing date April 29, 2002, indicates that there are five total claims pending. Accordingly, Applicants will apply the rejections in the Office Action to the claims as amended in the Preliminary Amendment.

Rejections under 35 U.S.C. § 112

Stereogenic Center

Claims 5, 9 and 56 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the claims allegedly lack antecedent basis because of the recitation of "stereogenic center" which is not recited in the main claims.

Claims 5 and 9 were canceled in the Preliminary Amendment. This rejection as applied to Claims 5 and 9 is moot.

With regard to the rejection of Claim 56, the claim has been amended to clarify that the carbon to which R_2 and $R_{2'}$ are attached is of the R configuration. Applicants respectfully request that the rejection be withdrawn.

Omnibus Type Claim

Claim 57 has been rejected under 35 U.S.C. §112, second paragraph as being indefinite in that it allegedly fails to point out what is included or excluded by the claim language. Claim 57 was cancelled in the Preliminary Amendment. Applicants respectfully maintain that this rejection is moot and request that it be withdrawn.

Methods of Screening

Finally, Claims 58 and 59 have been rejected as being substantial duplicates of each other since both recite "a method of screening . . . ". Again, both of these claims were cancelled in the Preliminary Amendment. Applicants respectfully maintain that this rejection is moot and request that it be withdrawn.

Rejections under 35 U.S.C. § 102(a)

A. Chenard

Claims 31, 32, 45, 49-55, and 57 have been rejected under 35 U.S.C. 102(a) as being anticipated by Chenard *et al.* EP 884,310 ("Chenard"). Claims 32, 49-52 and 57 were previously cancelled. Applicants maintain that this rejection is moot with respect to those claims. The rejection is respectfully traversed as applied to Claims 31 and 53-55.

The present invention is directed to a novel class of compounds having a core quinazolinone structure that are modulators of mitotic kinesins, and more particularly, modulators of the mitotic kinesin KSP. Applicants have amended the claims herein to focus on one embodiment of the present invention, namely, the quinazolinone amines of formula 1(d). These compounds can be used to inhibit human KSP; to treat diseases of proliferating cells; to develop inhibitors and modulators of KSP; and the like.

According to one embodiment, these compounds will have a chiral center at the stereogenic center bearing R_2 and $R_{2'}$; i.e., R_2 and $R_{2'}$ are different. In another embodiment, this chiral center is of the R configuration.

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a

person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdtn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974]).

Chenard is cited as described quinazolinone compounds that are embraced by the claimed formula[1] with $-NHR_4$ or $-NR_{3"}R_4$. Applicants respectfully disagree. Chenard teaches a quinazolin-4-one core structure having a substituent of the formula $-Y\text{-}Z\text{-}(BR^3R^4)$ wherein Y-Z can be either $-CH_2NH-$ or $-NHCH_2-$ and B is phenyl, pyridyl, or pyrmidyl. As such, Chenard does not teach or suggest any quinazolinone amines of formula 1d, as claimed herein. More specifically, Chenard does not teach or suggest any quinazolinones having either a chiral center or the tertiary amine substituent as claimed herein. Applicants submit that Chenard does not teach every element of the claims; therefore, that the invention, as claimed herein, is not anticipated by Chenard.

B. Spirkova

Claims 31, 32, 45, 49-55, and 57 have also been rejected as being anticipated by Spirkova *et al.* CA 132:35672 ("Spirkova"). Claims 32, 49-52 and 57 were previously cancelled. Applicants maintain that this rejection is moot with respect to those claims.

The rejection is respectfully traversed as applied to Claims 31 and 53-55.

Spirkova is described as teaching the compound 2-[(dimethylamino)methyl]- 4(1H)-quinazolinone. The cited references does not teach or suggest a quinazolinone amide of formula 1(d) having either the chiral center or the claimed substituent pattern. More specifically, as $R_{3"}$ cannot be hydrogen, the claimed genus does not encompass a (dimethylamino)methyl group appended to the quinazolinone core. As the elements of Spirkova are *not* the same as those presently claimed, Applicants submit that Spirkova does not anticipate the pending claims and respectfully request that this rejection be withdrawn.

C. Debnath

Claims 31-45, and 57 have been rejected as being anticipated by Debnath *et al.* (1999) J. Med. Chem. 42:3203-3209 ("Debnath"). Claims 32, 49-52 and 57 were previously cancelled. Applicants maintain that this rejection is moot with respect to those claims.

---

[1] Applicants note that the indicated claims do not encompass the formula $-N\ R_{3"}R_4$. Applicants will apply the rejections as to the formula $-N(CH_2\ R_{3"})R_4$.

The rejection is respectfully traversed as applied to Claim 31.

Debnath is said to disclose compounds labeled as ADS-J11, ADS-J12, ADS-J13, ADS-J14, and ADS-J16[2], which are allegedly embraced in the claimed invention when the quinazolinone is substituted with $-N(R_4)(C=O)R_3$. Applicants note that the formula comprising this substituent was cancelled from Claim 31 in the Preliminary Amendment. As such, the cited art does not anticipate the claimed invention. Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 31-55 and 57 have been rejected under 35 U.S.C. 102(b) as being anticipated by multiple references. Claims 32, 49-52 and 57 were previously cancelled. Applicants maintain that this rejection is moot with respect to those claims.

The rejection is respectfully traversed as applied to Claims 31 and 53-55. Each of the references cited in the Office Action is now addressed in turn.

A. Padia

Padia U.S. Patent No. 5,756,502 ("Padia") is cited for its teaching of Examples C, D, K, 1-4, 7, 8, etc. Applicants note that Examples C, D, K, 1-4, 7 and 8 do not fall within the scope of the claimed genus as they do not have a substituent comprising the formula $-N(CH_2R_{3''})R_4$. More specifically, they do not have a $-CH_2-$ group off of the sidechain amine. As such, the cited art does not anticipate the claimed invention. Applicants respectfully request that the rejection be withdrawn.

B. Bellina

Bellina *et al.* PCT Publication Number WO 98/26664 ("Bellina") has been cited for its teaching of compounds 18, 19, 81 and 127. Applicants respectfully note that Compound 18 has a $-CH_2SO_2-$ substituent appended to the quinazolinone core and thus, does not anticipate the claimed invention. Compound 19 does not anticipate the claimed invention as it is not a tertiary amine as claimed herein. Moreover, Compound 81 is a secondary amide (as opposed to the tertiary amine claimed herein.) Likewise, Compound 127 is a secondary amide and lacks a chiral center. As such the cited art does not anticipate the claimed invention.

---

[2] Applicants respectfully submit that the Examiner inadvertently included ADS-J16 in the rejection as it does not have a quinazolinone core. Assuming that a typographical error was made, Applicants have instead included ADS-J15 in their analysis.

C. Pandey

Pandey *et al.* CA 124:331723 ("Pandey") has been cited for its teaching of the compound N-[[3-(4-acetylphenyl)-3,4-dihydro-4-oxo-2-quinazolinyl]methyl]-benzamide. Again, as was found in Bellina, the cited compound is a secondary amide (rather than the claimed amine) and lacks a chiral center. As such, the cited art does not anticipate the claimed invention.

D. Parasharya

Parasharya et al. CA 121:108675 ("Parasharya") is said to teach compound 3-(4-hydroxyphenyl)-2-[(phenylamino)methyl]-4(3H)-quinazolinone. The cited compound does not anticipate the claimed invention as it is not a quinazolinone amine of formula 1(d). It does not have a tertiary amine side chain off the quinazolinone ring structure. The cited compound also lacks a chiral center, as claimed herein. As such, the cited art does not anticipate the claimed invention.

E. Saari

Saari *et al.* CA 117:19173 ("Saari") has been cited as teaching 2-[[(5-ethyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinyl)amino]methyl-quinazolinone. As with Parasharya, the cited compound lacks a tertiary amine side chain from the quinazolinone ring and a chiral center. Applicants, thus, maintain that the cited art does not anticipate the claimed invention.

F. Farghaly

The Office has cited Farghaly *et al.* CA 114:122242 ("Farghaly") for its teaching of 3-(4-chlorophenyl)-2-[[(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)amino]methyl]-4(3H)-quinazolinone. The cited compound does not bear a tertiary amine side chain or a chiral center and, as such, does not anticipate the claimed invention.

G. El-Nasser Ossman

El-Nasser Ossman *et al.* CA 106:207516 ("El-Nasser Ossman") has been cited for its teaching of 4-[(3,4-dihydro-4-oxo-3-phenyl-2-quinazolinyl)methyl]amino-benzenesulfonamide. As with Farghaly, the cited compound does not have a tertiary amine side chain. As such, the cited art does not anticipate the claimed invention.

H. Rao

Rao *et al.* CA 105:97416 ("Rao") has been cited for its teaching of 6,8-dibromo-2-[(dimethylamino)methyl]3-(4-methylphenyl)-quinazolinone. The cited compound lacks a chiral center and as such, does not anticipate the claimed invention. Moreover, as $R_{3''}$ cannot be hydrogen, the claimed genus does not encompass a (dimethylamino)methyl group appended to the quinazolinone core. As the elements of Rao are *not* the same as those presently claimed, Applicants submit that Rao does not anticipate the pending claims.

I. Kumar

Kumar *et al.* CA 102:142800 ("Kumar") describes 3-phenyl-2-[[(2-phenylethyl)amino]methyl]-quinazolinone. This compound has a secondary amine side chain rather than the tertiary amine side chain as claimed herein. The cited compound also lacks a chiral center. As such, the cited art does not anticipate the claimed invention.

J. Chaurasia

Chaurasia *et al.* CA 96:6681 ("Chaurasia") is said to teach 3(2-benzothiazolyl)-2-[2-(diethylamino)ethyl]quinazolinone, monohydrochloride. Again, this compound has a (diethylamino)ethyl side chain rather than the claimed optionally substituted amino methyl sidechain substituent. The cited art does not anticipate the claimed invention.

K. Tani

Tani *et al.*CA 93:26374 ("Tani") has been cited for its teaching of 6-amino-2-[(diethylamino)methyl]-2-(2-methylphenyl)-quinazolinone. Because this compound has a substituted methylene group appended to the quinazolinone core, it does not have a chiral center as claimed herein. As such, Tani does not anticipate the claimed invention.

L. Ager

Ager *et al.* CA 86:83505 ("Ager") is said to describe 2-[[(1,1-dimethylethyl)amino]methyl]-3-(2-methylphenyl)-quinazolinone. The cited compound has a secondary amine side chain and lacks a chiral center. It does not teach every element of the claims; therefore, the invention is not anticipated by Ager.

M. Gupta

Gupta *et al.* CA 69:42637 ("Gupta") has been cited for its teaching of 2-(2-hydrazinoethyl)-3-phenyl-quinazolinone. The cited compound does not have a secondary amine side chain or a chiral center. As such, the reference does not anticipate the claimed invention.

N. Singh

Singh *et al.* CA 92:58712 ("Gupta") has been cited for its teaching of 3-[3-[[bis(2-chloroethyl)amino]methyl]-4-hydroxyphenyl]-2-[[bis(2-hydroxyethyl)amino]methyl]-quinazolinone. The cited reference lacks a chiral center. As such, the cited art does not anticipate the claimed invention.

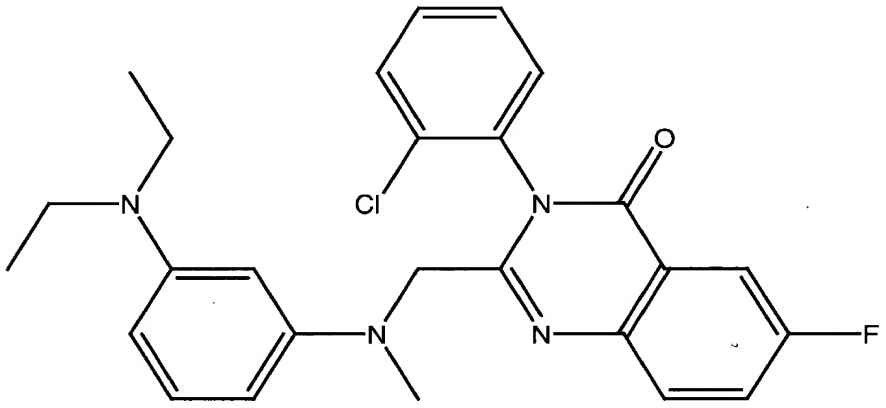
Rejections under 35 U.S.C. § 102(e)

Claims 31, 32, 45, 49-55, and 57 have been rejected under 35 U.S.C. 102(e) as being anticipated by Chenard *et al.* U.S. Patent No. 6,136,812 ("Chenard"). Claims 32, 49-52, 55 and 57 have been cancelled. Applicants maintain that this rejection is moot with respect to those claims.

The rejection is respectfully traversed as applied to Claims 31 and 53-54.

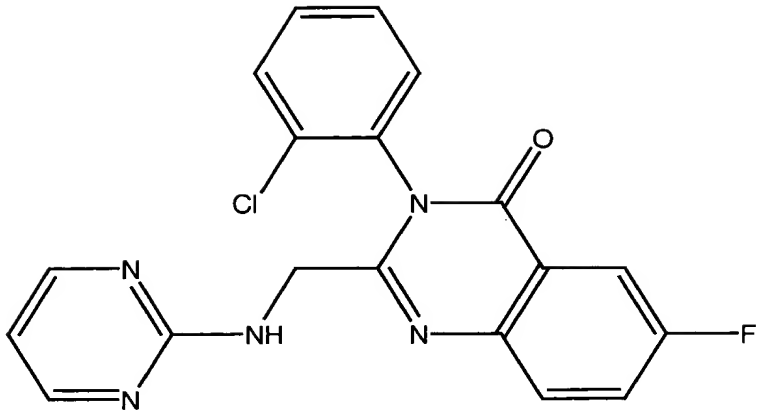
The Office has cited Chenard for its teaching of the compounds on lines 31-51 of Column 28. Each of these compounds is discussed in turn.

3-(2-Chloro-phenyl)-2-[(3-diethylaminomethylphenylamino)-methyl]-6-fluoro-3H-quinazolin-4-one



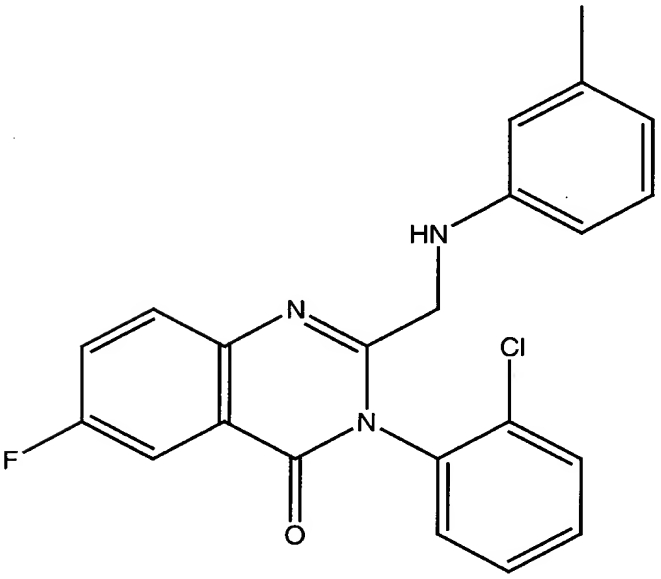
lacks a chiral center.

3-(2-Chloro-phenyl)-6-fluoro-2-(pyrimidin-2-ylaminomethyl)-3H-quinazolin-4-one



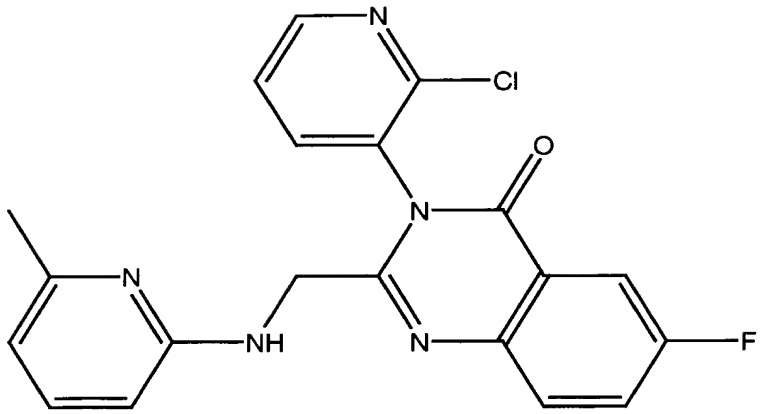
also lacks a chiral center. In addition, it does not have a tertiary amine side chain.

3-(2-Chloro-phenyl)-6-fluoro-2-(m-tolylaminomethyl)-3H-quinazolin-4-one



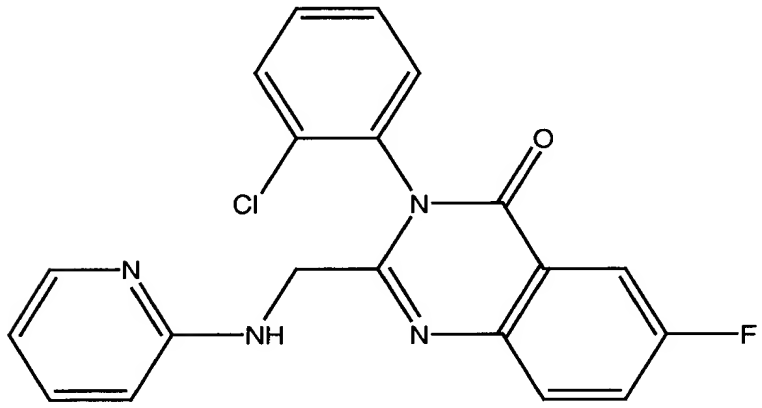
lacks a chiral center and a tertiary amine side chain.

3-(2-Chloro-pyridin-3-yl)-6-fluoro-2-[(6-methyl-pyridin-2-ylamino)-methyl]-3H-quinazolin-4-one



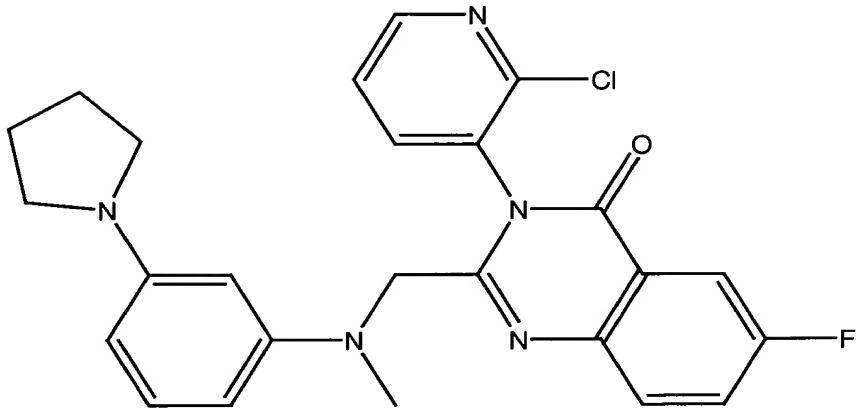
again lacks a chiral center and a tertiary amine side chain.

3-(2-Chloro-phenyl)-6-fluoro-2-(pyridin-2-ylaminomethyl)-3H-quinazolin-4-one



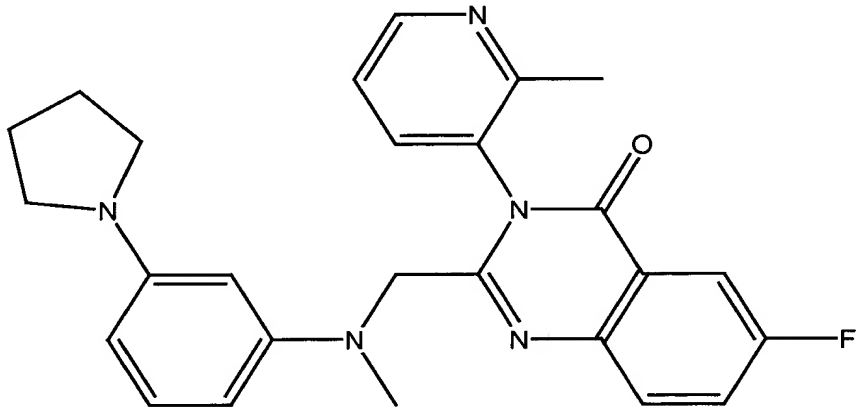
lacks a chiral center and a tertiary amine side chain.

3-(2-Chloro-pyridin-3-yl)-6-fluoro-2-[(3-pyrrolidin-1-ylmethyl-phenylamino)-methyl]-3H-quinazolin-4-one



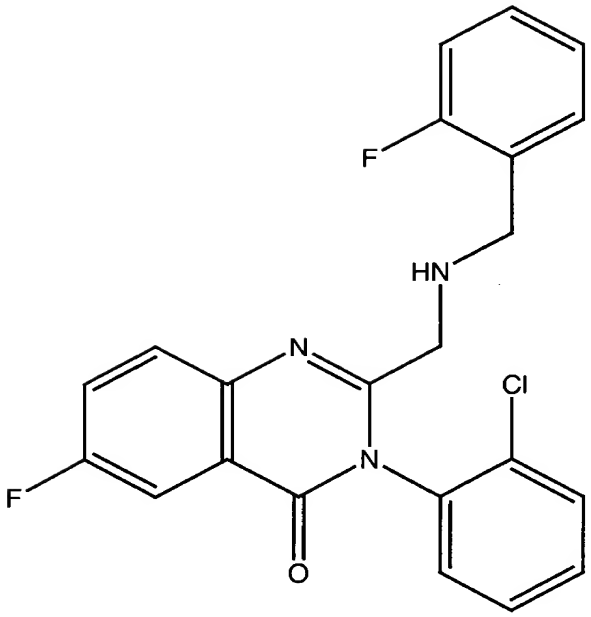
lacks a chiral center.

6-Fluoro-3-(2-methyl-pyridin-3-yl)-2-[(3-pyrrolidin-1-ylmethyl-phenylamino)-methyl]-3H-quinazolin-4-one



also lacks a chiral center.

3-(2-Chloro-phenyl)-6-fluoro-2-[(2-fluoro-benzylamino)-methyl]-3H-quinazolin-4-one



lacks a chiral center and a tertiary amine side chain. As such, the cited reference does not teach every element of the claims and does not anticipate the claimed invention.

Rejections under 35 U.S.C. § 102(f)

Claims 31-56 have been rejected under 35 U.S.C. §102(f) as the applicant allegedly did not invent the claimed subject matter because Applicants had previously purchased various compounds. Applicants have carefully reviewed the list of commercial compounds. Applicants believe that none of such compounds fall within the scope of the claimed invention. Moreover, the commercial compounds were provided as-is and without any excipients and more particularly, without any pharmaceutically acceptable excipients.

Applicants respectfully request that the Examiner point to those specific compounds in the list that allegedly anticipate the claimed invention. In the absence of any specific arguments by the Examiner, Applicants respectfully submit that the claimed invention is not anticipated by the list of commercial compounds. Applicants request that the rejection be withdrawn.

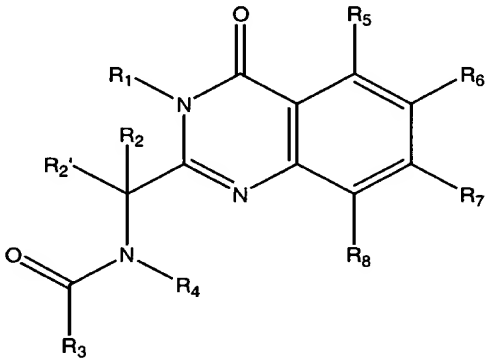
Rejections under 35 U.S.C. § 103

Claims 1-30 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Padia in view of Bisset *et al.* U.S. Patent No. 5,561,133 ("Bisset"). Claims 1-30 were previously

cancelled. Applicants maintain that this rejection is moot with respect to those claims. Applicants respectfully request that the rejection be withdrawn.

Double Patenting

Claims 31-45, 56, and 57 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34-44, 56, and 60-71 of copending Application No. 09/699,047. Applicants note that the claims of the '047 application were previously amended to focus on one of the embodiments of the present invention, i.e., the quinazolinone amides of formula:



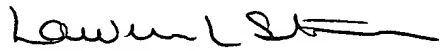
Applicants respectfully maintain that the scope of the claims in the '047 application do not overlap with the scope claimed in the present invention. Applicants respectfully request that this rejection be withdrawn.

Claims 31-45, 56 and 57 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31, 32, 34-45 and 56 of copending Application No. 09/724,712 Applicants note that the '712 application is abandoned. Applicants request that this rejection be withdrawn.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP

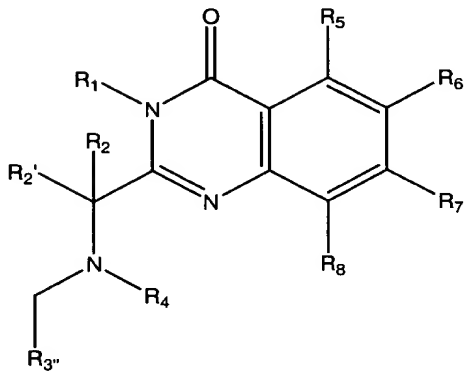


Lauren L. Stevens
Reg. No. 36,691

P.O. Box 778
Berkeley, CA 94704-0778

MARKED UP VERSION OF AMENDED CLAIMS

31. (Twice amended) A compound having the following structure:



wherein:

R_1 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_2 and R_2' are independently chosen from hydrogen, alkyl, oxaalkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl; or R_2 and R_2' taken together form a 3- to 7-membered ring**, provided that R_2 and $R_{2'}$ are different**;

[R_3 is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, oxaalkyl, oxaalkylaryl, substituted oxaalkylaryl, $R_{15}O$- and R_{15}-NH-;

$R_{3'}$ is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl and R_{15}-NH-;]

$R_{3''}$ is chosen from alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_4 is chosen from [hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, substituted alkylheteroaryl, and R_{16}-alkylene-;] **lower alkyl; cyclohexyl; phenyl substituted with hydroxy, lower**

alkoxy or lower alkyl; benzyl; substituted benzyl; heterocyclyl; heteroarylmethyl; heteroarylethyl; heteroarylpropyl and R_{16}-alkylene, wherein R_{16} is di(lower alkyl)amino, (lower alkyl)amino, amino, lower alkoxy, or N-heterocyclyl; and

R_5, R_6, R_7 and R_8 are independently chosen from hydrogen, alkyl, alkoxy, halogen, fluoroalkyl, nitro, dialkylamino, alkylsulfonyl, alkylsulfonamido, sulfonamidoalkyl, sulfonamidoaryl, alkylthio, carboxyalkyl, carboxamido, aminocarbonyl, aryl and heteroaryl[;

R_{15} is chosen from hydrogen, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, substituted alkyl, substituted aryl, substituted alkylaryl, substituted heteroaryl, and substituted alkylheteroaryl;

R_{16} is chosen from alkoxy, amino, alkylamino, dialkylamino, N-heterocyclyl and substituted N-heterocyclyl;

with the proviso that when R_3 is R_{15}-NH- attached to carbonyl, both of R_2 and R_4 must be other than hydrogen].

56. (Twice Amended) A compound according to any of claims **31 or** 53 to 55 wherein the [stereogenic center] **carbon** to which R_2 and $R_{2'}$ are attached is of the R configuration.